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Paraganglioma of the filum terminal: Case report and review of the literature

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ABSTRACT

Paraganglioma of the filum terminal/cauda equina is a rare slow growing tumor which originates from the ectopic sympathetic neurons. Surgically, total excision may be difficult for this well demarcated tumor surrounded by couple of rootlets but is usually possible in nearly all cases. Actually, final diagnosis cannot be determined intraoperatively, but is possible only after an immunohistochemical staining. Herein, the authors present a middle age woman whose initial symptoms were lower back pain and radiculopathy. Her MRI was found to be compatible with a cauda equina tumor. During her excisional surgery a hard and relatively vascular tumor was fully removed. The Immunohistochemical results were compatible with paraganglioma of the filum terminale. In addition to case presentation, thorough review of the literature is also done.

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1. Introduction

Paraganglioma is a neuro-endocrine tumor which is derived from the embryonic sympathetic and parasympathetic nervous system [1,2]. About 90% of paragangliomas arise within the adrenal gland and the remaining 10% are extra-adrenal [1–4]. Extra-adrenal paragangliomas are classified as either spinal or extra-spinal [3,4]. Extraspinal paragangliomas have parasympathetic origins and are most often located within the carotid body and glomus jugular [1,3]. Spinal paragangliomas are quite rare and have sympathetic origins [3–5]. They frequently appear in two different locations and may either occur in the bony component of the vertebral column or originate from the filum terminal growing in between the rootlets of the cauda equina [5,6]. Cauda equina paraganglioma (CEP) is a solid, highly vascularized, slowly growing and well encapsulated tumor [3–5].

The first example of a paraganglioma of the filum terminale was reported by Miller and Torack in 1970 and was designated as secretory ependymoma [7]. However, the first author that used the term of paraganglioma were Lerman et al. in 1972 [8]. Gutenberg et al. in a review of the literature in 2009 could encounter 215 cases with cauda equina or filum terminale paraganglioma. We updated the

literature could encounter 104 new cases including a case of our own.

2. Case report

A 48-year old Caucasian woman was admitted with lower back pain, a left sciatica, and a needle pin-prick sensation of the lower extremities. She had no fecal or urinary incontinence. Neurological examination disclosed only a mild decrease in the force of the extensor of the left foot. Sagittal T1 and T2-weighted spinal MRI showed a well-delineated intradural isointense mass extending from T12 to the upper edge of L2. The tumor measured 6 cm in length (Fig. 1). In a T1-weighted Gadolinium enhanced MRI a homogenous tumor was clearly demonstrated. There were a few flow voids on the upper pole of the mass that were indicative of the high vascularity of the tumor (Fig. 2). Surgical intervention was proposed and was done by senior author (Prof. AR).

Under general anesthesia and the patient in prone position, a laminectomy of T12, L1 and upper half of L2 were performed. After a dural opening, a dark meat colored mass which was surrounded by a couple of rootlets was also identified. Initially, the surrounding rootlets were draped from the mass and this was associated with an alternative shrinkage of the tumor through the use of bipolar cautery. The procedure was continued till the mass became completely separated from the rootlets. Then, the filum terminale which was protruding out from the lower pole of the mass was identified due to its distinctive appearance. At this stage the coagulation and excision of the filum permitted a gross total removal of the tumor (Fig. 3). The post-operative course was uneventful and during a 6-

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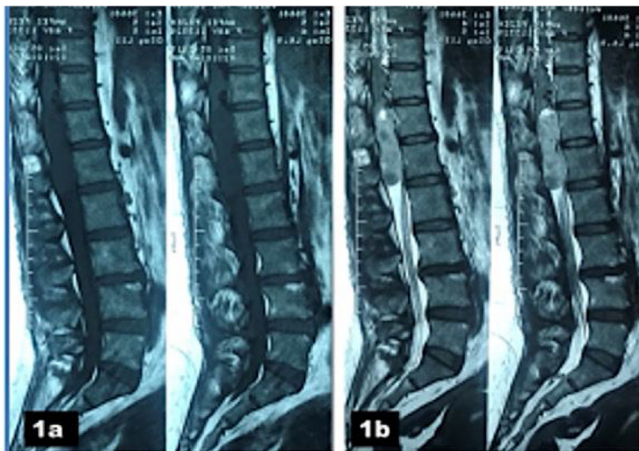


Fig. 1. Sagittal MRI of the lumbosacral spine. There is an intradural extramedullary mass extending from T12 to L1. (a & b) both in T2- and T1-weighted images the mass is isointense.

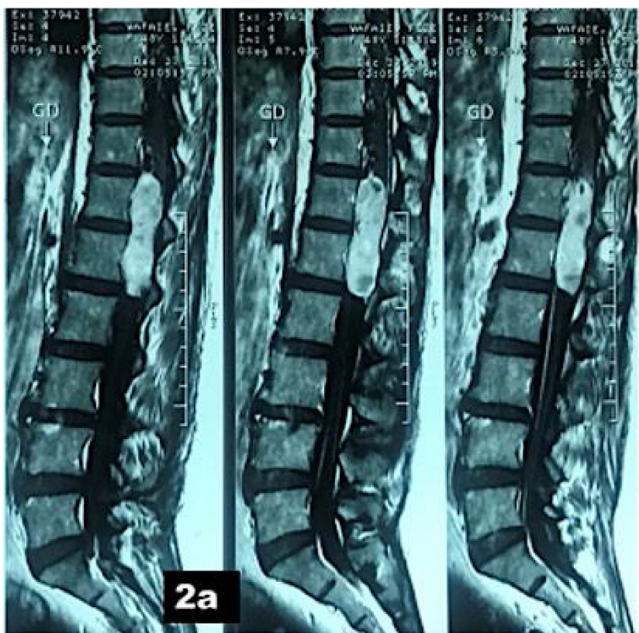


Fig. 2. In gadolinium enhanced sagittal lumbar MRI the tumor shows homogenous enhancement.



Fig. 3. Photograph of the shrunken tumor by bipolar cautery after gross removal.

month follow-up encounter the patient was found to be doing well and free from any neurological symptoms.

Histopathologic examination with Hematoxylin and Eosin (H&E) showed cellular perivascular arrangement which looked like 'pseudorosettes' similar to ependymoma (Fig. 4A). But, in retrospect, taken together these histologic findings, radiologic features and intraoperative solid as well as vascular appearance of the tumor which were not typical for a myxopapillary ependymoma, further survey was done which displayed chief cells with granular amophilic cytoplasm and spheroidal nuclei, separated by fine fibrovascular septae and many dilated blood vessels, suggestive of the 'Zellballen' pattern of paraganglioma (Fig. 4B).

Thereafter, immunohistochemical labeling with chromogranin and synaptophysin was done. Immunostaining for tumor cells with chromogranin was positive suggesting paraganglioma (Fig. 4C). Immuno-labeling of the tumor cells with synaptophysin marker was also positive confirming the diagnosis of paraganglioma (Fig. 4D).

In further survey, focal staining sustentacular cells with S100 protein marker that is a typical finding in paraganglioma was positive (Fig. 5A). Staining for tumor cells with pan-cytokeratin marker which is only positive in myxopapillary ependymoma showed negative result (Fig. 5B). Also, negative reaction of tumor cells to EMA marker ruled-out ependymoma (Fig. 5C). Finally, negative reaction of tumor cells to GFAP marker confirmed paraganglioma (Fig. 5D).

3. Discussion

Extra-adrenal pheochromocytoma are called as paraganglioma [1–4]. Paragangliomas of the filum terminale are rare benign tumors that arise from the ectopic sympathetic neurons and become misplaced within the rootlets of cauda equina or on the filum terminale [3,4]. However, dorsolumbar intradural paraganglioma originate from the proximal filum terminale, rather than the cauda equina rootlets. However, for these tumors, both paraganglioma of the filum terminale or cauda equina can be used. Paragangliomas are naturally slow growing, well-demarcated, intradural, hypervascular and solid tumors that neither infiltrates the conus nor the rootlets and are histologically equivalent to WHO grade I [9].

We updated the review from 2009 until October 2020 and could find 104 new cases including a case of our own [10–46]. Adding these cases to 215 previously reported cases reported in Gutenberg's survey, the total number of the cases reached to 319 (Table 1).

With consideration of both reviews, 192 out of 319 cases were males and the remaining 127 were females. Indicating male predominance, with a rate of 1.5 to 1. The age of patients at the time of diagnosis varied from 9 to 77 years with the mean age of 49 [7].

3.1. Clinical picture

These tumors are slow growing and become symptomatic by local compression. The most common presenting symptom is low back pain that could be accompanied by radiculopathy with or without motor deficit [3,4,9,10,16,22,26,30,46–49]. Neurological deficits vary from partial foot drop to paraparesis. Sexual dysfunction and sphincter disturbance are uncommon [27].

Apoplectic cauda equina syndrome is rare and usually represents intratumoral hemorrhagic event. Intra-parenchymal bleeding may occur spontaneously or might be secondary to the use of oral anticoagulants [9,15,35,38,41].

Subarachnoid hemorrhage as an initial presenting symptom is extremely rare in CEP [50].

Despite the neuroendocrine origin of these tumors, the majority of all cauda equina paragangliomas are functionally non-secretory.

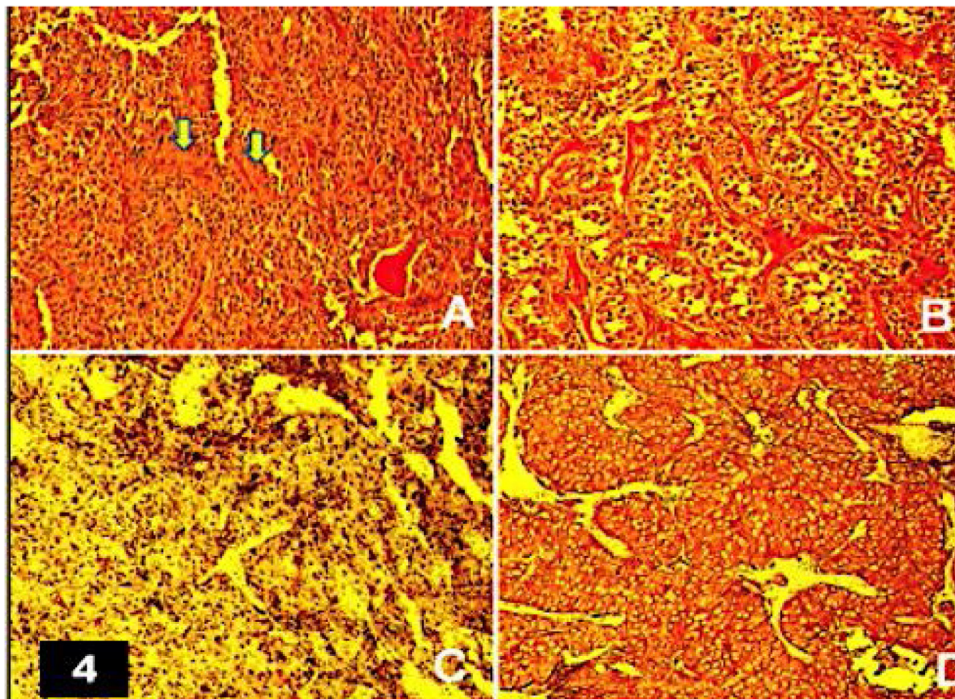


Fig. 4. (a) tumor cells show focal perivascular arrangement similar to ependymoma (Arrows), H&E. stain '200 (b) Nests of clear cells (Zellballen) that are characteristic of paraganglioma. H&E. stain '200 (c) positive immunostaining for tumor cells with chromogranin suggesting paraganglioma. IHC stain '200 (d) Positive immunostaining for tumor cells with synaptophysin marker suggesting paraganglioma. IHC stain '200.

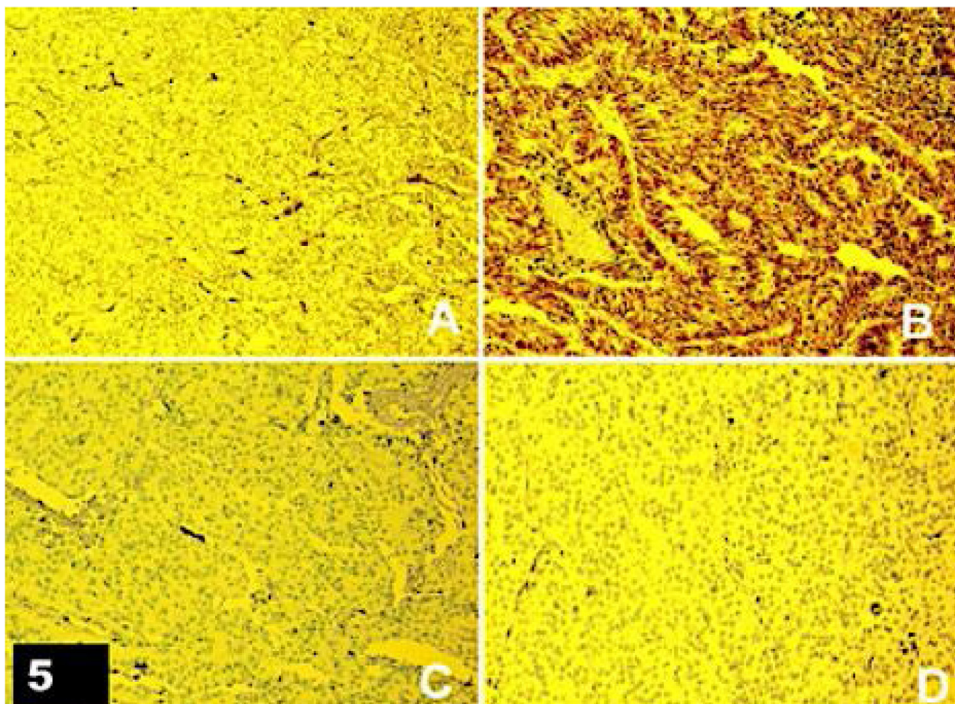


Fig. 5. (a) focal staining sustentacular cells with S100 marker that is a typical finding in paraganglioma. IHC stain '100 (b) Positive staining for tumor cells with pan-cytokeratin marker which is unusual findings in paragangliomas other than filum terminale ones. IHC stain '200 (c) Negative reaction of tumor cells to EMA marker. This finding actually rules-out ependymoma IHC stain '200 (d) Negative reaction of tumor cells to GFAP marker. IHC stain '200.

This means that systemic symptoms of catecholamine activity such as paroxysmal hypertension are quite rare in this particular tumor [3,4,9,36,51–53].

The signs and symptoms of increased intracranial pressure (RICP) with papilledema probably due to elevated protein contents have been reported rarely in CEPs [12,54–58]. Furthermore, symp-

toms of normal pressure hydrocephalus (NPH) has been described in one occasion [21].

3.2. Imaging

Magnetic resonance imaging is the tool of choice for the diagnosis of the paragangliomas of the cauda equina and filum ter-

Table 1

Updated review of reported cases on “Paraganglioma of the filum terminale”.

No	Author	Year	Sex	Age
1	Hsieh et al.[85]	2009	F	48
2	Marcol et al.[27]	2009	M	43
3	Oo et al.[47]	2009	M	26
4	Landi et al.[48]	2009	M	49
5	Demircivi et al.[59]	2010	M	75
6	Shankar et al.[18]	2010	M	47
7	Rhee et al.[21]	2010	M	70
8	Henaux et al.[31]	2011	F	40
9	Henaux et al.[31]	2011	F	37
10	Henaux et al.[31]	2011	M	54
11	Henaux et al.[31]	2011	M	72
12	Henaux et al.[31]	2011	M	47
13	Henaux et al.[31]	2011	F	55
14	Henaux et al.[31]	2011	F	33
15	Ardon et al.[49]	2011	M	37
16	Ardon et al.[49]	2011	M	41
17	Ardon et al.[49]	2011	M	51
18	Mathon et al.[46]	2012	F	35
19	Mathon et al.[46]	2012	M	77
20	Mathon et al.[46]	2012	F	60
21	Mathon et al.[46]	2012	F	63
22	Mathon et al.[46]	2012	M	57
23	Mathon et al.[46]	2012	F	72
24	Hong et al.[53]	2012	F	47
25	Agrawal et al.[36]	2012	M	50
26	Kinge et al.[68]	2012	M	42
27	Ma et al.[35]	2012	M	51
28	Midi et al.[86]	2012	F	38
29	Matsumoto et al.[37]	2012	M	50
30	Matsumoto et al.[37]	2012	M	54
31	Fulare et al.[13]	2013	F	60
32	Bush et al.[12]	2013	M	72
33	Mishra et al.[26]	2014	F	40
34	Mishra et al.[26]	2014	M	44
35	Mishra et al.[26]	2014	M	50
36	Mishra et al.[26]	2014	F	34
37	Mishra et al.[26]	2014	M	54
38	Mishra et al.[26]	2014	M	46
39	Mishra et al.[26]	2014	M	58
40	Mishra et al.[26]	2014	M	77
41	Khan et al.[87]	2014	M	73
42	Oh et al.[14]	2014	f	76
43	Reddy et al.[22]	2014	F	54
44	Sable et al.[78]	2014	M	58
45	Woo et al.[38]	2014	M	60
46	Kalani et al.[39]	2015	M	54
47	Corinaldesi et al.[11]	2015	F	33
48	Yang et al.[16]	2015	M	48
49	Yang et al.[16]	2015	M	46
50	Yang et al.[16]	2015	F	44
51	Yang et al.[16]	2015	M	20
52	Yang et al.[16]	2015	F	55
53	Yang et al.[16]	2015	F	48
54	Yang et al.[16]	2015	M	54
55	Yang et al.[16]	2015	M	69
56	Yang et al.[16]	2015	F	22
57	Yang et al.[16]	2015	F	35
58	Yang et al.[16]	2015	M	49
59	Yang et al.[16]	2015	F	54
60	Yang et al.[16]	2015	M	46
61	Yang et al.[16]	2015	M	75
62	Yang et al.[16]	2015	M	66
63	Yang et al.[16]	2015	M	27
64	Yang et al.[16]	2015	M	38
65	Yang et al.[16]	2015	M	68
66	Yang et al.[16]	2015	F	43
67	Simsek et al.[30]	2015	M	40
68	Simsek et al.[30]	2015	M	36
69	Dillard-Cannonet al.[10]	2016	M	32
70	Jain et al.[40]	2016	M	40
71	Akbik et al.[88]	2016	M	68
72	Hilmani et al.[89]	2016	F	74
73	Nagarjun et al.[15]	2016	F	36
74	Murrone et al.[41]	2017	M	56
75	Thomson et al.[33]	2017	F	61

Table 1 (Continued)

No	Author	Year	Sex	Age
76	Adam et al.[45]	2018	F	48
77	Wang et al.[77]	2018	M	36
78	Turk et al.[25]	2018	F	64
79	Turk et al.[25]	2018	F	28
80	Turk et al.[25]	2018	M	54
81	Turk et al.[25]	2018	F	54
82	Turk et al.[25]	2018	F	46
83	Turk et al.[25]	2018	M	62
84	Turk et al.[25]	2018	M	40
85	Turk et al.[25]	2018	M	61
86	Mendez et al.[90]	2019	M	75
87	Ghedir et al.[43]	2019	M	64
88	Nagose et al.[24]	2019	M	42
89	Honeyman et al.[23]	2019	M	45
90	Fiorini et al.[34]	2020	M	53
91	Fiorini et al.[34]	2020	F	42
92	Fiorini et al.[34]	2020	M	32
93	Fiorini et al.[34]	2020	M	60
94	Fiorini et al.[34]	2020	M	62
95	Fiorini et al.[34]	2020	F	41
96	Fiorini et al.[34]	2020	F	53
97	Fiorini et al.[34]	2020	M	38
98	Fiorini et al.[34]	2020	F	34
99	Fiorini et al.[34]	2020	F	56
100	Fiorini et al.[34]	2020	M	68
101	Fiorini et al.[34]	2020	M	66
102	Fiorini et al.[34]	2020	M	55
103	Fiorini et al.[34]	2020	F	62
104	Rahimizadeh et al.[76]	2020	F	48

minale [3–5,46,49,59–65]. Hay et al. were the first who described the MRI appearance of the filum terminal paragangliomas, in 1989. Paragangliomas of the filum are isointense or a mixture of isointense-hypo intense, both in T1-weighted and in T2-weighted MRI. indicate a hyper vascularity of the paraganglioma [3]. A salt-and-pepper appearance in T1-weighted images which become reverse in T2-Weighted sequences also indicate different stages of an intratumoral hemorrhage and its resolution with time [16].

Nonetheless, the tumors show homogenous hyperintensity in a Gadolinium enhanced MRI. Intratumoral serpentine flow-voids, in particular at the upper pole is due to hypervascularity of the tumor [3–5,46,49,59]. Coexistence of a large cyst with CEP has been described in two cases [45,66]. The superficial siderosis over the surface of a CEP displaying a hypointense line is secondary biosynthesis of ferritin [67,68]. Association of CEP with syringomyelia has been observed in one patient by Steel, in 1994 [69].

Although, MRI findings are not pathognomonic, but they do help to narrow the differential diagnosis of CEP from ependymomas and schwannomas.

Bozkurt, et al. in 2004 described a silk cocoon appearance in spinal angiography as a pathognomonic feature of CEP, although a final diagnosis is ultimately dependent on immunohistopathological results [70]. In highly vascular paragangliomas, preoperative embolization has been advocated by Rodesch et al., although this procedure does not seem necessary unless cauda equina hemangioma is suspected [71].

3.3. Differential diagnosis

Actually, paragangliomas have no pathognomonic features and might be easily mistaken with schwannomas, ependymomas [72–74]. Furthermore, meningioma, hemangiomas, teratomas, and metastases should be judiciously included in a differential diagnosis [75,76].

Surgical intervention: The tumor can be accessed after a laminectomy of the corresponding levels and dural opening. These tumors are well demarcated but the surrounding rootlets should be carefully stripped off the mass under appropriate magnification.

Alternative shrinkage of the tumor with bipolar cautery will facilitate this stage of the procedure. Once the tumor is free and detached from all surrounding rootlets, the filum should then be identified, coagulated, and incised. This will permit the total removal of the tumor [1–4,25,31,48,59]. Rarely, during tumor manipulation and excision by the surgeon; an unexplained paroxysmal hypertension resistant to any hypotensive agents might be experienced. Management of this complication without properly diagnosing the underlying functional paraganglioma is difficult issue and might be fatal [36]. Hopefully, hypertension is relieved after the complete removal of the tumor [36].

Surgical Management:

In surgical intervention the goal should be total removal of the tumor. Subtotal resection often leads to recurrence, and postoperative radiation therapy for patients with incomplete resection has no effect on prevention of recurrences.

3.4. Pathology

The specimens should be fixed with 4% neutral formaldehyde solution and then subjected to hematoxylin and eosin (H&E) staining and immunohistochemical labeling.

In routine H&E staining, paraganglioma shows pseudopapillary pattern with thick hyalinizing fibrous trabeculae, quite like myxopapillary ependymoma [1–4]. However, paragangliomas are comprised of two cell types, chief cells arranged in lobules surrounded by spindle shaped sustentacular cells, which are classically described as having a “Zellballen” pattern, all surrounded by a delicate capillary network [15,37,39,41,48].

Pathologically, ependymoma is characterized by perivascular ‘pseudorosette’, radially oriented cell groups surrounding small vessels quite similar to paragangliomas. In order to differentiate these two pathologies several staining methods can be used [37,39].

Glial fibrillary acidic protein (GFAP) staining is one of these methods that can be used to differentiate these two pathologies. Accordingly, ependymal cells are GFAP positive whereas GFAP staining is negative in neoplastic cells of paragangliomas [3,4,10–16,19,20,22,26,29,30,32,33,37–41,45].

Nonspecific enolase (NSE) is a sensitive marker of chief cell, but it lacks specificity, because it might become positive in tumor cells of ependymomas. With this staining method, immunoperoxidase stain labels the cytoplasm of the chief cells into granular and diffusely dark brown [4].

However, final diagnosis of paragangliomas can be made with immunohistochemical labeling with chromogranin, synaptophysin and S100 [77]. Chief cells are reactive for synaptophysin and chromogranin where sustentacular cells can be identified by immunoreactivity to S-100 [4,39,77]. In synaptophysin and chromogranin, the dot-like chief cells becomes diffusely brown where in S100 staining the protein of the sustentacular cells are labeled brown.

A small number of paragangliomas may contain mature ganglion cells in addition to the sustentacular cells, this type is designated as cauda equina gangliocytic paraganglioma [5,8,18,24,26,40,78]. Histologically, in gangliocytic paragangliomas, neurofilament staining is present in spindle cells along with ganglion cells confirming a gangliocytic variation of a paraganglioma. The origin of this variation remains unclear, although it is generally believed that gangliocytic paragangliomas originate from neuroectodermal ganglion cells [5,8,18,24,26,40,78].

Co-existence of paraganglioma and ependymoma has been reported in rare instances [83,84]. In such cases, these two tumors were physically separated and histopathologically were quite distinct.

3.5. Outcome

With the total removal of the tumor the chance of recurrence is almost nil [16,25,26,31,34,46,49]. Rarely, with subtotal removal, malignant transformation of paraganglioma may occur, so similar to other malignant tumors might be associated with intraspinal, intracranial, and distant metastasis [40,79–83].

Leptomeningeal dissemination of a paraganglioma of the filum terminale has been reported in one occasion [33].

The manuscript has been written and submitted with respect to SCARE checklist [84].

4. Conclusion

Spinal paragangliomas are a very rare entity that often present with low back pain and sciatica. Their clinical course is generally benign and the symptoms are resolved soon after the gross total resection of the tumor. Magnetic resonance with Gadolinium administration gives useful information for surgical planning but is not diagnostic. The total removal of the tumor is usually possible in the vast majority of the cases with patience and use of magnification. Patients in whom complete removal has been not feasible will require an assiduous long-term set of. Follow-up encounters.

Declaration of competing interest

None to declare!

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Ethical approval

Approved!

Consent

Written informed consent was obtained from the patient for publication and corresponding images.

Author contribution

Abolfazl Rahimizadeh:
Conception and design
Acquisition and data
Analysis and interpretation of data
Drafting of the manuscript
Critical revision of the manuscript for important intellectual content
Supervision
Seyed Ali Ahmadi:
Acquisition and data
Analysis and interpretation of data
Administrative, technical or material support
Abdolreza Mohammadi Koshki:
Acquisition and data
Analysis and interpretation of data
Administrative, technical or material support
Ava Rahimizadeh:
Analysis and interpretation of data
Drafting of the manuscript
Mona Karimi:
Conception and design

Critical revision of the manuscript for important intellectual content

Registration of research studies

This article is a case report!

Guarantor

Abolfazl Rahimizadeh.

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